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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/412,947	10/05/99	AGRAWAL S	HYZ-050CP

HM12/1024

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EXAMINER
EPPS, J

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/412,947	Agrawal
Examiner	**Group Art Unit**
Janet Epps	1635

☒ Responsive to communication(s) filed on *Oct 5, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-33* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Drawings

1. The drawings are objected to by the Draftsperson under 37 CFR 1.84 or 1.82 for the reasons set forth on the attached PTO-948. Correction is required.

Specification

2. Page 48, lines 27-28, of the specification contains illegible text, appropriate correction is required.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The post office address should include the ZIP Code designation.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

Applicant's request for benefit of the earlier filing date of application 08/532,979, September 22, 1995, is not granted. The disclosure of 08/532,979 does not provide sufficient support for the

method claimed in the instant application. Parent application, 08/532,979 discloses the use of modified antisense oligonucleotides targeting protein kinase A subunit RI-α and a method for treating cancer comprising the administration of said antisense oligonucleotides in combination with an additional unspecified chemotherapeutic agent. However, the instant application claims a method for treating cancer comprising the administration of said antisense oligonucleotides in combination with an antibody that binds to EGFR or a cytotoxic agent selected from the group consisting of taxanes, platinum-derived agents, and topoisomeraseII-selective drugs. The parent application does not provide specific guidance or support for practicing the claimed method comprising the use of an antibody that binds to EGFR or a cytotoxic agent selected from the group consisting of taxanes, platinum-derived agents, and topoisomeraseII-selective drugs.

The disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 1-3, and 7-11 are rejected under 35 U.S.C. 102(a) as being by Tortora et al.

Tortora et al. describe the synergistic inhibition of human cancer cell growth by the combination of cytotoxic drugs and mixed backbone antisense oligonucleotides targeting protein kinase A. Tortora et al. specifically disclose a mixed backbone oligonucleotide (HYB 190) of the following sequence and comprising the following modifications: (G-sp-C-sp-G-sp-T-sp-G-sp-C-sp-C-P-deoxy-P-methyl-T-P-deoxy- P-methyl-C-P-deoxy-P-methyl-C-P-deoxy-P- methyl-T -P-deoxy- P-methyl-C-sp-A-sp-C-sp-T-sp -G-sp-G-sp-C) . Furthermore, this reference teaches that protein kinase A type I plays a key role in neoplastic transformation conveying mitogenic signals of different growth factors and oncogenes. Inhibition of protein kinase A type I by antisense oligonucleotides targeting its RI-α regulatory subunit results in cancer cell growth inhibition. The novel mixed backbone oligonucleotide HYB 190 and its mismatched control HYB 239 were tested on soft agar growth of several human cancer cell types. HYB 190 demonstrated a dose-dependent inhibition of colony formation in all cell lines whereas the HYB 239 at the same doses caused a modest or no growth inhibition. A non-inhibitory dose of each mixed backbone oligonucleotide was used in OVCAR-3 ovarian and GEO colon cancer cells to study whether any cooperative effect may

occur between the antisense and a series of cytotoxic drugs acting by different mechanisms. Treatment with HYB 190 resulted in an additive growth inhibitory effect with several cytotoxic drugs when measured by soft agar colony formation. A synergistic growth inhibition, which correlated with increased apoptosis, was observed when HYB 190 was added to cancer cells treated with taxanes, platinum-based compounds., and topoisomerase II selective drugs. This synergistic effect was also observed in breast cancer cells and was obtained with other related drugs such as docetaxel and carboplatin. Combination of HYB 190 and paclitaxel resulted in an accumulation of cells in late S-G2 phases of cell cycle and marked induction of apoptosis. A cooperative effect of HYB 190 and paclitaxel was also obtained in vivo in nude mice bearing human GEO colon cancer xenografts. These results are the first report of a cooperative growth inhibitory effect obtained in a variety of human cancer cell lines by antisense mixed backbone oligonucleotide targeting protein kinase A type I-mediated mitogenic signals and specific cytotoxic drugs.

Tortora et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 12, 23, and those claims dependent therefrom, recites the phrase "capable of down-regulating the expression of", the term "capable of" as used in this context renders these claim(s) indefinite because the capacity of a compound to perform some function is merely a latent characteristic of said compound and said language carries no patentable weight. See MPEP § 2173.05(b), (d) and (g).

9. Claims 1, 12, and 23 recite the limitation "the expression of". There is insufficient antecedent basis for this limitation in these claims.

10. Claim 3 recites the limitation "the nucleotide sequence" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

11. Claims 13-22 recite the limitation "[t]he method" in claim 12. There is insufficient antecedent basis for this limitation in these claims.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting proliferation of cancer cells *in vitro*, does not reasonably provide enablement for treatment of cancer in a patient *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons given in the following rejection.

14. Claims 12-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 12-33 read on pharmaceutical compositions comprising modified oligonucleotides capable of down regulating the expression of protein kinase A subunit RI-α and a second agent comprising an antibody that binds EGFR or a cytotoxic agent, and methods for treating cancer in a subject comprising administering said pharmaceutical compositions.

The specification as filed does not provide sufficient guidance and or instruction that would allow one of skill in the art to practice the instant methods or use the claimed pharmaceutical compositions throughout the full scope of the claimed invention without undue experimentation. This conclusion is based upon the lack of working *in vivo* examples demonstrating wherein Applicants were successful in treating cancer in an individual by practicing the claimed methods or using the claimed pharmaceutical compositions. The specification only provides *in vitro* methods demonstrating the efficacy of the claimed compositions for inhibiting the proliferation of cancer cells.

There are a variety of factors which complicate antisense oligonucleotide based therapy that have not been overcome by routine experimentation. Some of these factors include delivery of antisense/ribozyme compounds *in vivo,* wherein the compositions are delivered to the appropriate target tissue and are effective in the treatment of a condition associated with the expression of a gene; providing a means to make available a desired level of antisense oligonucleotide to the desired tissues for a sustained period of time so that a condition can be treated; and predicting the behavior of the

antisense oligonucleotide once inside a cell. Crooke (1998), states that "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke describes a variety of factors which influence cellular uptake and distribution of antisense base therapeutics, such as: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also describes the effects of non-antisense effects, such as protein binding, for example phosphorothioate modified antisense oligonucleotides tend to bind to many proteins, such protein binding may influence cell uptake, distribution, metabolism and excretion of the antisense oligonucleotide. In addition, such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3).

Branch (1998) also teach that "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes to their specified target *in vivo* is unpredictable, the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Antisense therapy is a highly unpredictable and field and the skill in the art is high.

Both Branch and Crooke teach that the behavior of antisense based pharmaceuticals are unpredictable, therefore claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, the specification does not describe the pharmaceutical compositions and methods of treating cancer in an individual by administration of said pharmaceutical compositions comprising the oligonucleotides of the instant invention, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the delivery and behavior of antisense *in vivo* and further with secondary effects such as treating a disease associated with the expression of a gene, the lack of guidance provided in the specification as filed in this regard, and the breadth of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

October 23, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER